BNL Radioisotope Research Status and Plans
Science & Technology Review November 2014

L. F. Mausner
Collider Accelerator Department,
Brookhaven National Laboratory
Upton, NY

BROOKHAVEN NATIONAL LABORATORY

Overview of Program non Production Activities

- **Radionuclide R&D (Nuclear reactions, targetry research, chemical process and generator development)**
  - Summary of FY13-14 effort
    - Ac-225 development
    - Ge-68 process modification
    - Pt isotopes
    - As-72 development (FOA funded)
  - Plans for the future

- **Training**
  - Support (space, equipment, faculty) for DOE funded Nuclear Chemistry Summer School, an undergraduate course in nuclear and radiochemistry
  - Loss of DOE funding will cause cessation after 25 years of operation here

- **Radiation damage studies**
  - Target and magnet materials for Fermi Lab & LHC (LARP)
  - Materials for Facility Rare Isotope Beams (FRIB)

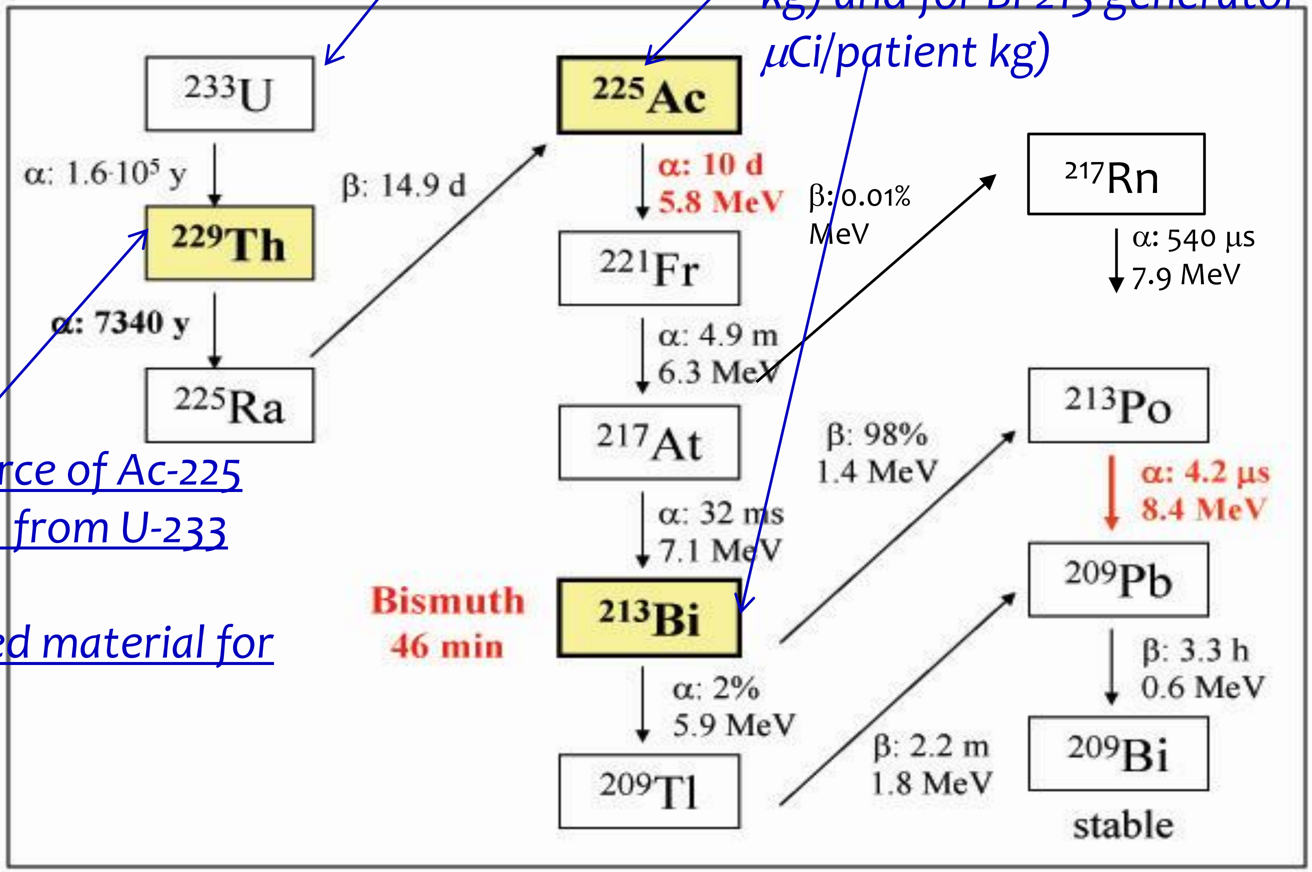
Development of Ac-225 production

- Ac-225 as an in-vivo generator and as a source of Bi-213 has shown promise in early radioimmunotherapy clinical trials against leukemia.
- Properties:$T_{1/2}$=10.0 d, 4 alpha particles emitted, mean $E\alpha$= 5.9 MeV, $E\gamma$ (keV): 99.7 (2.9%)
- Current need to support clinical trials 50Ci/yr
- Present global supply ~1.2 Ci annually from decay of Th-229 (mostly from an existing ORNL generator)
- In response to the shortage of Ac-225, a collaboration between Brookhaven, Los Alamos, and Oak Ridge National Laboratories initiated an investigation of an alternative production approach.

Ac-225 decay chain (Neptunium Series)

National depository of U-233 is at ORNL

Ac-225 for direct use (<5 μCi/patient kg) and for Bi-213 generator (~1000 μCi/patient kg)

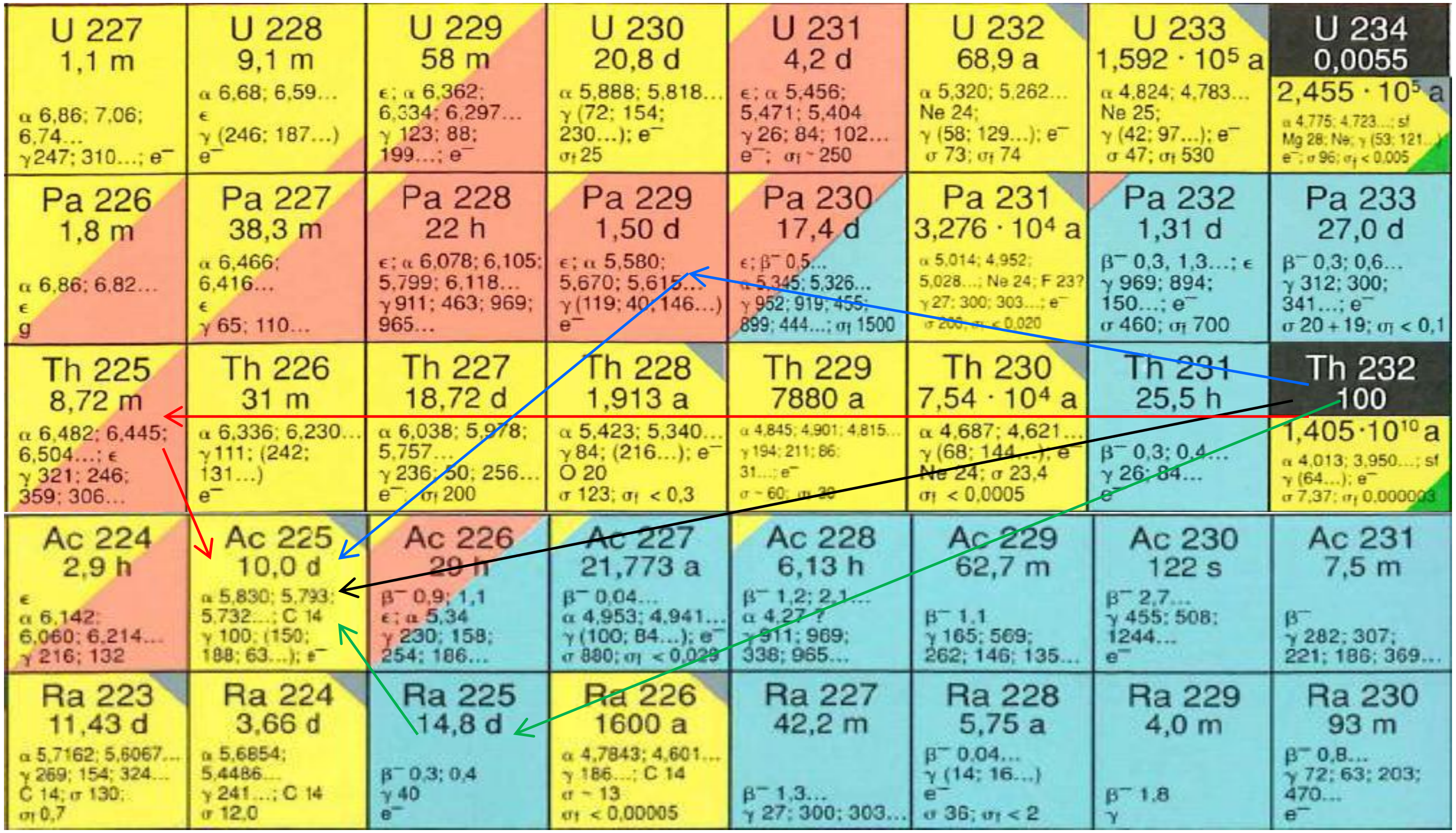


Present source of Ac-225
Separate Th from U-233 (ORNL)
Th-229 is feed material for Ac-225

An alternative method: $^{232}Th(p,spall)^{225}Ac$

- Advantages
  - Predicted high production yield
  - Frequent batch production possible
  - Production at both BNL and LANL provides year round supply
- Disadvantages
  - High proton energy needed
  - Very large number of isotopes coproduced (~200 produced at greater than 100µCi predicted by MCNPX calculations)
  - Complex chemistry required
  - Safety issues due to high radiation dose and extra control of contamination and emissions needed for the α emitters

High energy route to Ac-225



Production routes

$^{232}Th(p,x)^{225}Ac$

$^{232}Th(p,x)^{225}Th \rightarrow ^{225}Ac$

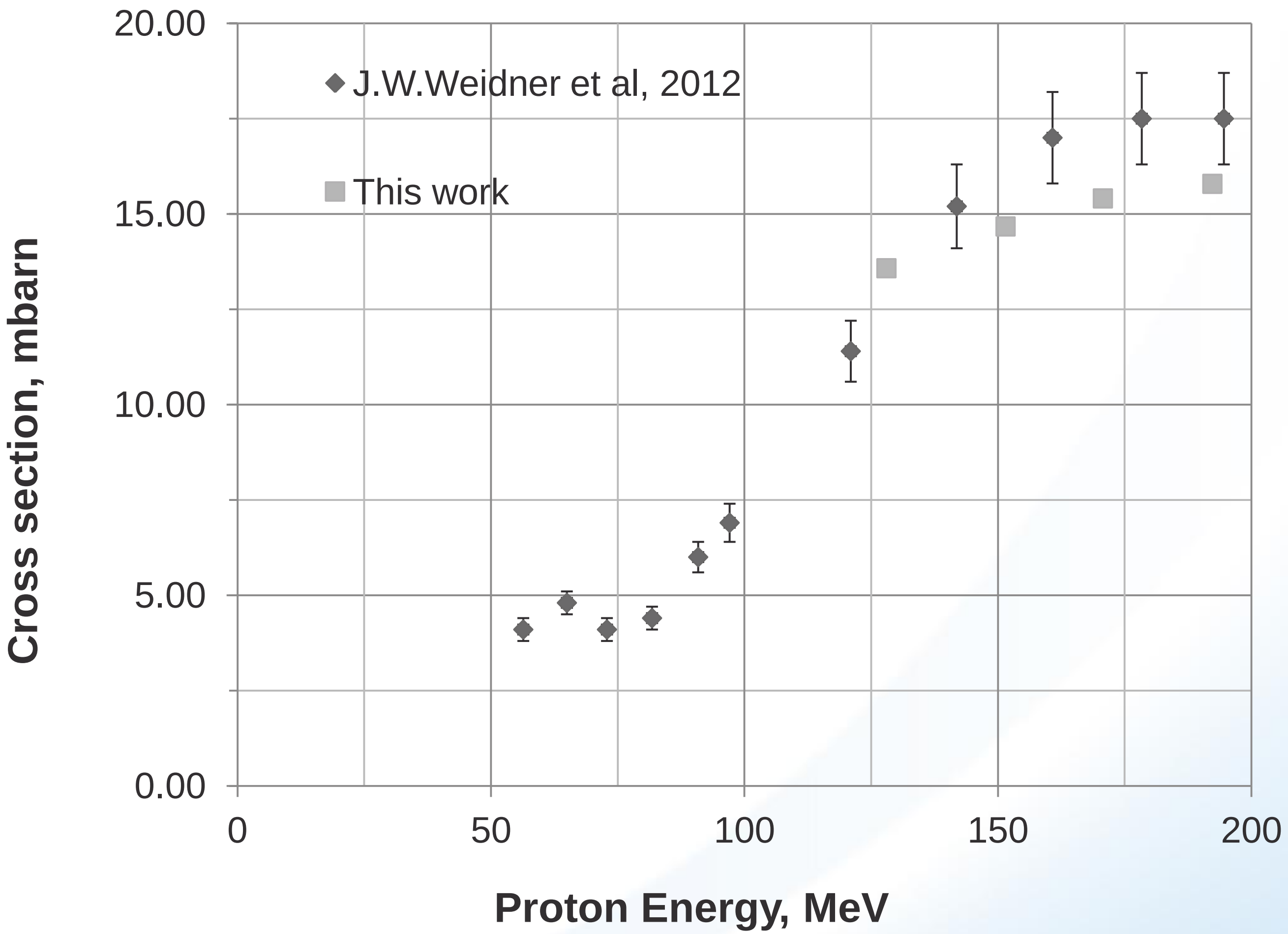
$^{232}Th(p,4n)^{229}Pa \rightarrow ^{225}Ac$

$^{232}Th(p,x)^{225}Ra \rightarrow ^{225}Ac$

Pre-Stage 1 Effort to Date

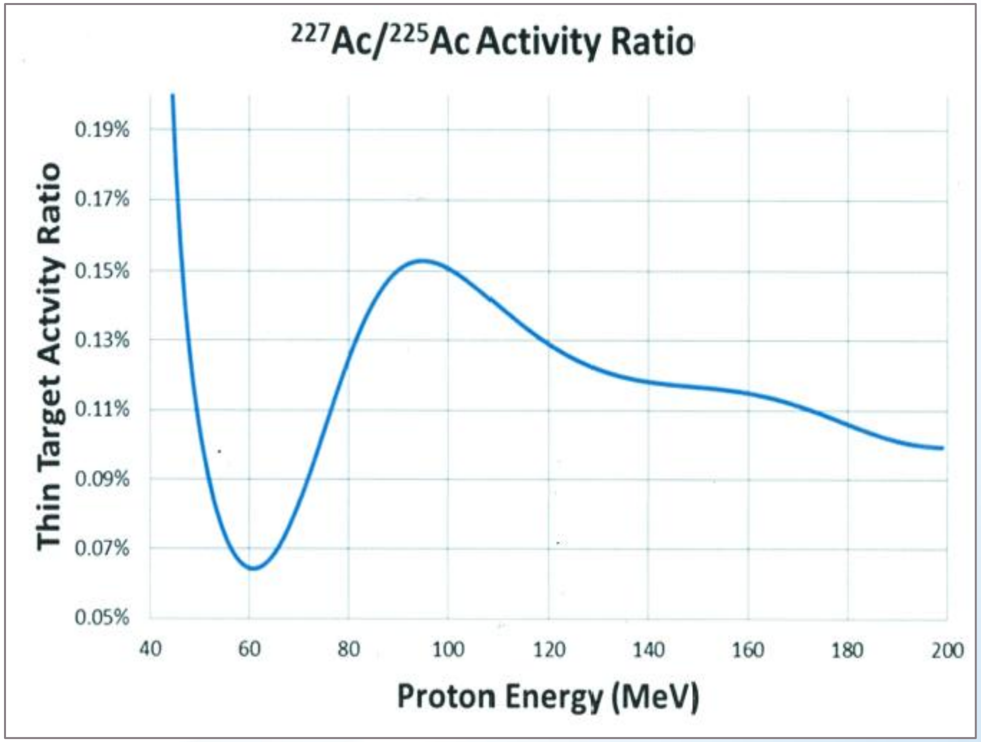
- BNL: One to three high purity Th foils (obtained commercially), each 0.125mm thick, were encapsulated in a bolted Al container.
  - Th can react with air at high temperature, so the target was assembled in a helium filled glove box and then He leak tested.
  - A total of 11 irradiations at 128, 152, 171, & 192 MeV for durations of 3 hours up to 9 days, at beam intensity of 40-115μA were performed.
    - Two runs were for chemistry development and internal evaluation, 5 were for external user evaluation and 4 were for nuclear excitation function and radiopurity determination.
    - The Th foils were shipped to ORNL same day for short runs or after 7 days of decay for long runs.
- ORNL: Processed all targets, measured yields and cross sections, and shipped to users.
  - A maximum of 40mCi of Ac-225 delivered to end users (BNL#10) which exceeds minimum Project Stage 1 goals (5-50mCi) but is only 33% of EOB radioactivity (total of 14 days decay and ~85% chemical recovery).

Ac-225 Cross sections



Challenges Associated with Accelerator Derived ^{225}Ac : Unavoidable ^{227}Ac Content

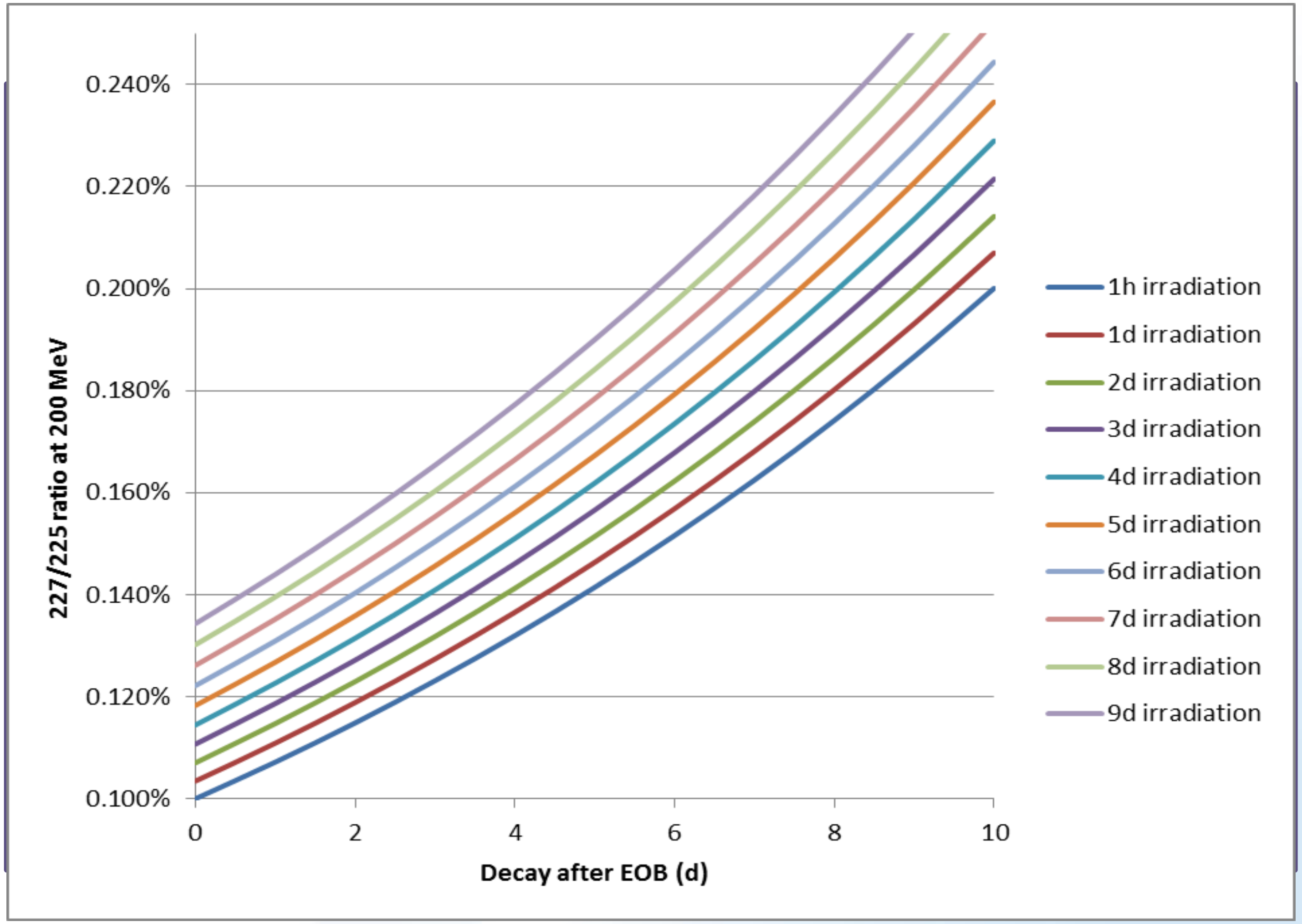
- **Production of ^{225}Ac also results in the co-production of ^{227}Ac ($t_{1/2}$ = 21.8 y). Ratio improves at higher proton energy, but degrades with longer irradiations.**



Instantaneous activity ratio of ^{227}Ac to ^{225}Ac for a thin Th target as a function of proton beam energy. Note that beam energy range captures current capabilities at BNL's BLIP and LANL's IPF facilities.

Factors That Impact The $^{227}Ac/^{225}Ac$ Ratio

- Irradiation Conditions: energy, duration,….
- Target Design: thickness, …
- Process logistics: hold times after irradiation, chemical process duration, shipping times are the dominant factor in final delivered ratio.
- **Time is not an ally!**



Radionuclide yield for [p,xn], [p,pxn], [p,2pxn], [p,3pxn] reactions on ^{232}Th target (BNL#6 527mg/cm^2, E= 192 MeV, I= 69 μA)

Nuclear Reactions	Radionuclides	Half-life (d)	Irradiation Time (h)		
			EOB Yield mCi	Saturation Yield [μCi/μA/(mg/cm^2)]	Cross section mb
[p,xn]	Pa-228	0.92	ND	ND	
	Pa-229	1.40	ND	ND	
	Pa-230	17.40	11.38	1.22	2.35
	Pa-233	26.9	38.85	3.92	.94
[p,pxn]	Th-227	18.72	99.90	10.4	27.5
	Th-228	697.15	ND	ND	
	Th-229	2.68E+06	ND	ND	
	Th-231	1.06	ND	22.7	51.7
[p,2pxn]	Ac-225	10.0	113.6	7.36	16.78
	Ac-226	1.20	NM	6.36*	17.00
	Ac-227	7946	0.15	5.95	13.57
[p,3pxn]	Ra-223	11.43	29.45	2.04	4.65
	Ra-224	3.66	221.2	7.53	17.17
	Ra-225	14.8	6.01	0.51	1.17

Other Accelerator-Derived ^{225}Ac Concerns – Radiolanthanides and Fission Products

- Modeling and experiment suggest that appreciable quantities of lanthanides such as ^{139}Ce, ^{141}Ce, ^{143}Ce, and ^{140}La will be coproduced. Similar chemical behavior to Ac.
- <u>Many</u> other fission products (including Mo-99) are produced presenting new chemistry and QA challenges

Selected Fission products from 192 MeV protons on Th (BNL#6)

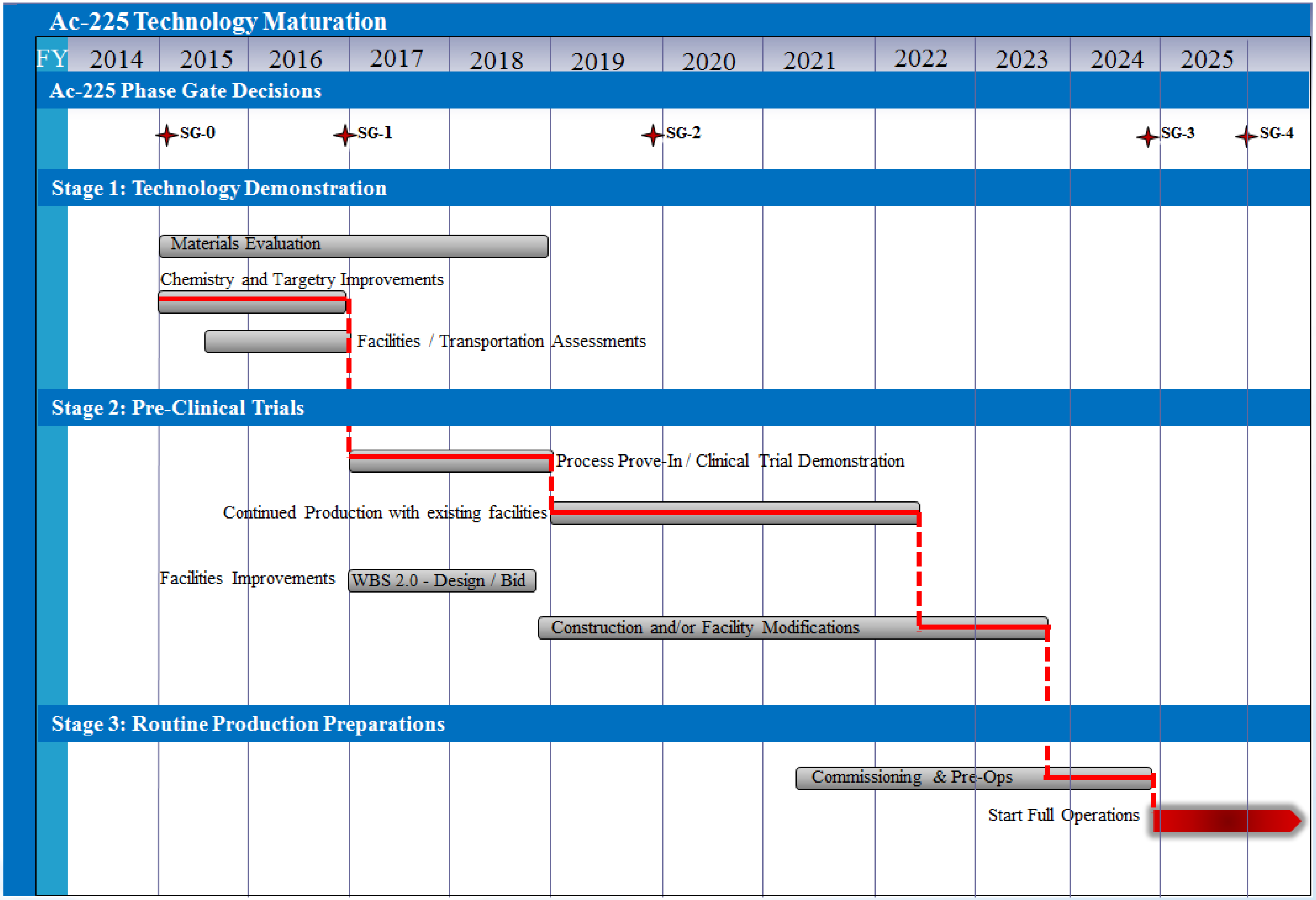
Radionuclides	Half-life (d)	Irradiation Time 190 h	
		EOB Yield mCi	Cross section mb
Zr-95	64.03	6.83	5.19
Nb-95	34.99	12.83	5.52
Mo-99	2.75	507.5	36.7
Ru-103	39.26	67.58	32.4
Ru-106	372.3	17.93	76.5
Ag-111	7.45	328.0	39.3
Sn-117m	13.61	18.77	3.50
Sb-124	60.21	8.92	6.40
Sn-125	996.5	33.70	7.28
Sb-126	12.4	37.10	6.48
Te-129m	33.6	14.00	5.80
I-131	8.02	56.30	7.10
Ba-131	11.5	40.01	6.58
Cs-136	13.2	25.80	4.73
La-140	1.68	45.70	2.97
Ce-141	32.5	26.45	10.63

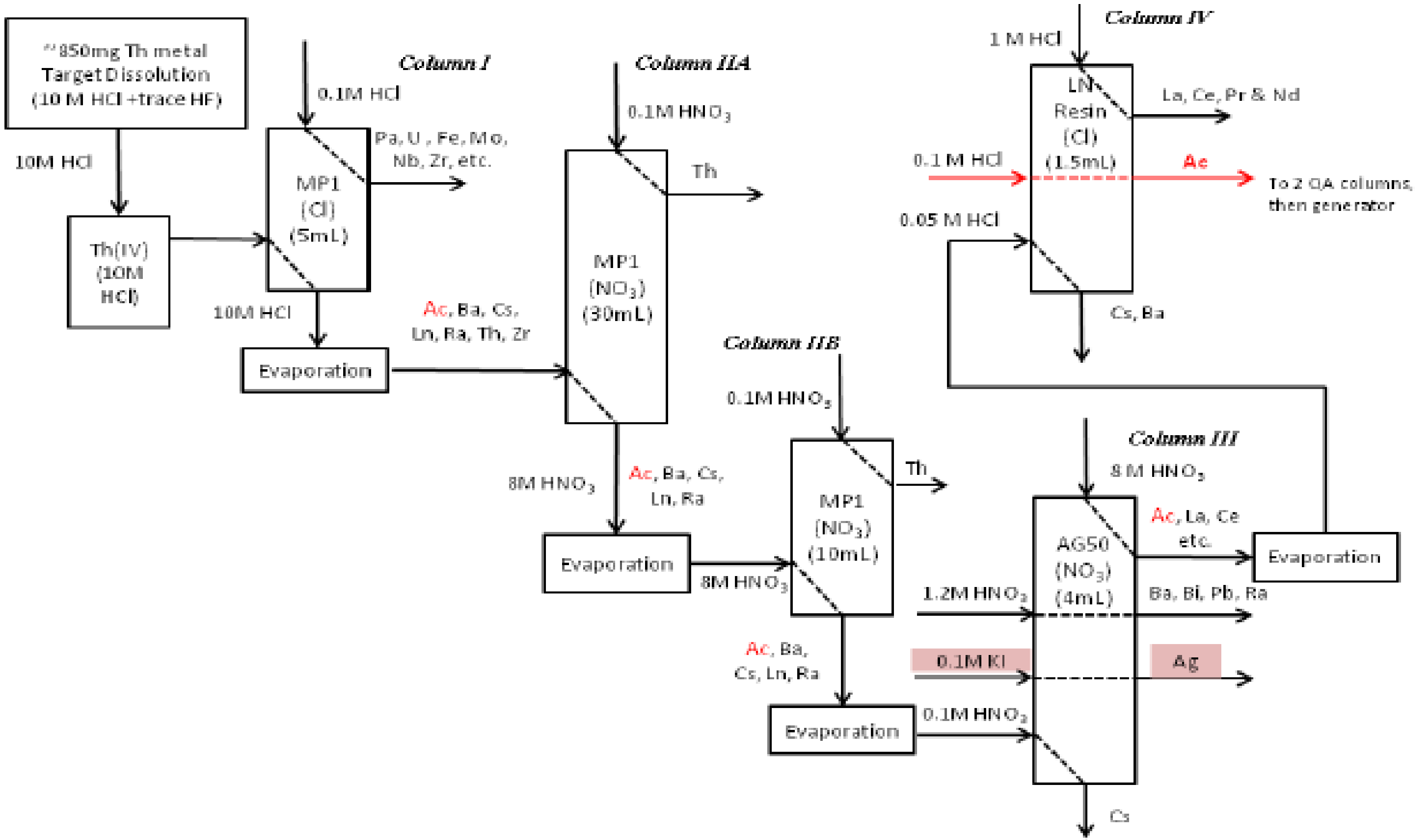
Production Summary and Conclusions to date

- Ac-225 cross section and production yield increase with increasing proton energy.
  - Irradiations with only 0.015” (0.38mm) thick Th foils produced 123mCi at EOB of Ac-225 in ~9 day irradiations.
  - Curie level production in 7-10d irradiation should be achievable with use of thicker Th targets. Thermal analysis and design of thicker targets or multiple thinner targets is underway.
- Ac-225/Ac-227 ratio improves with increasing energy.
  - EOB impurity level of ~0.15% should be achievable in routine production. Evaluation of the maximum acceptable level of Ac-227 for direct use is underway. Less important for use as Bi-213 generator.
- Ratio of total fission product to Ac-225 radioactivity is ~12:1.

Pre-Stage 1 Effort Conclusions

- ORNL generator prepared with accelerator produced Ac-225 appears to give equivalent elution performance and Bi-213 quality as Th-229 derived material.
- Chemical acceptability of accelerator produced Ac-225 looks good based on initial labeling studies.
- Delivery of 5mCi (LANL) to 40mCi (BNL) of Ac-225 to end users has been demonstrated. Further increase is limited by lack of a DOT Type B cask.
- Acceptability of Ac-227 content is not yet known, both from a toxicity issue and for waste disposal by users.
    - Independent dosimetry studies from biodistribution data needed.
- To assure tri-lab coordination DOE has requested that the program be more formally managed under project management guidelines. The national project manager is Dr. Kevin John of LANL. An official project review was held in Germantown on October 1-3, 2014. Responses to report recommendations are being prepared. Final Project Management Plan will be submitted by 12/15/14.

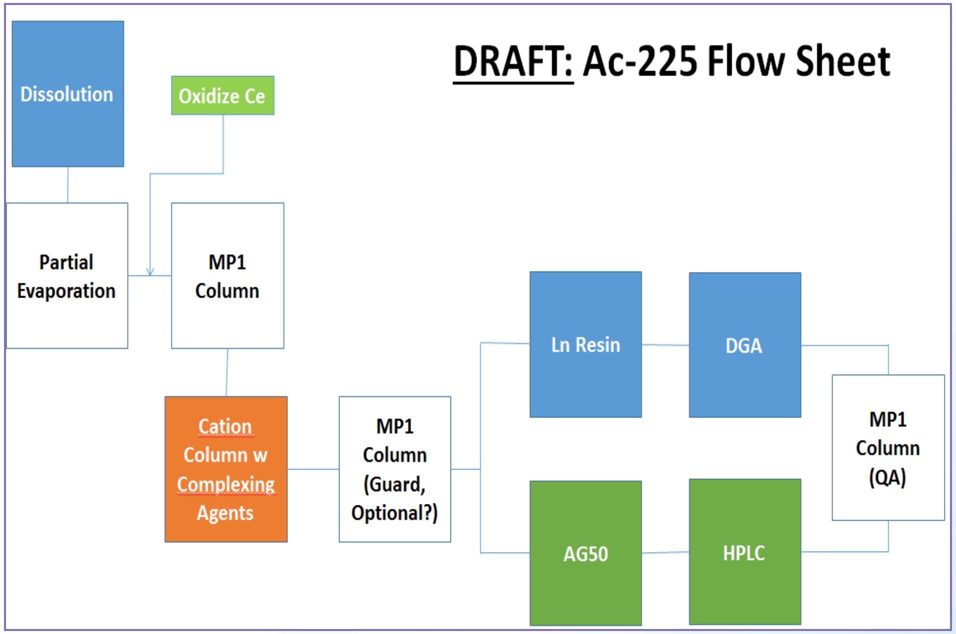

Ac-225 Technology Maturation
FY 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025
Ac-225 Phase Gate Decisions
SG-0
SG-1
SG-2
SG-3
SG-4
Stage 1: Technology Demonstration
Materials Evaluation
Chemistry and Targetry Improvements
Facilities / Transportation Assessments
Stage 2: Pre-Clinical Trials
Process Prove-In / Clinical Trial Demonstration
Continued Production with existing facilities
Facilities Improvements
WBS 2.0 - Design / Bid
Construction and/or Facility Modifications
Stage 3: Routine Production Preparations
Commissioning & Pre-Ops
Start Full Operations



ORNL Ac separation flow chart

BNL role in Ac-225 Stage 1 (FY15-17)

- FY15-Irradiate Th foils (~3-10g) and ship to ORNL to support user materials evaluation
- FY15-Coordinate with LANL to design larger scale Th targets (50-100g; 2-4mm thick, EBW sealed), [BNL core R&D]
- FY15- Investigate improved use of cation column (orange box) with Th complexing agents to replace multiple large anion columns in ORNL process using only Th, stable surrogate isotopes, and Ac-225 spike (hot cell not required). [BNL core R&D]
- FY16,17-Test 50g target designs at increasing beam current/duration and implement production with continued shipment to ORNL.
- FY16,17-Test cation chemistry with 10-50g Th and Ac-225 tracer (<1mCi); integrate into overall process & test at ORNL. [BNL core R&D]
- FY15,17- To support Ac-225 processing here in FY18 need to complete physical assessments of BNL facilities & upgrade needs, ES&H analysis (SAD, NESHAPS, NEPA, etc.), develop waste management plan, develop transportation plan.
- Progression to Stage 2 is not assured, but is dependent on Stage 1 results, market survey, and DOE/NP funding.



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Ac-225 separation development
Future Research

- Safety approval
  - Experimental safety documentation has been written

Future experiments

- Introduce Th and Ac and other metals into the mix of metals
- Perform ratio studies of Th to complexing agents (tartrate and citrate)
- Evaluate pH 3 load solution – La may elute and Ac may be retained
- Rinse with 3 M HCl (5-10 BV) to determine if La can be eluted and Ac retained
- Scale up
- Process an irradiated Th target

Other recent R&D: Ge-68 process modification

Goals :

To eliminate use of toxic organics in separation in order to qualify the Ge-68 to be used for a clinical Ge-68/GA-68 generator

Method: replace solvent extraction with resins for purification → AG1/Sephadex G25

Minimize # of columns → 1or 2 columns

Purify without evaporation of solvent → no evaporation

Meet DOE Product specs

Product in 0.1 M HCl → Ge-68 final product in 0.1 M HCl

Ge-68 conc.> 50 mCi/ml → 54-260 mCi/ml

No Zinc-65 in product

Ge-68 Separation Method –J. Fitzsimmons

Irradiated Gallium metal

↓ Leaching: ~4 M HCl, H_2O_2

Ge, Ga, Zn in ~4 M HCl, H_2O_2

PM4 ↓ Dilute to ~ 1.5 M HCl

$\boxed{\text{1. AG-1 Column}}$ → Retained Zn

↓ adds ~ 15 min.

Ge, Ga, Zn in HCl

↓ 1M Citrate, pH 12
add 10 M NaOH adjust pH to ~12.5

Ge-68 Retained ← $\boxed{\text{2. Sephadex G-25 column (Sigma)}}$

↓ 3 BV 0.1 M HCl

Pure Ge-68

↓ Rinse
5 BV 1 M Citrate pH 12.5
5 BV 0.001M Citrate pH 12.5
10 BV 0.03 M NaOH pH 12.5
1 BV Water

Eluted Ga, Zn

BV=bed volumes

Production of Platinum Isotopes – S.Smith & USNDP and U Mass Lowell

- Currently **≈50% of cancer patients** receive platinum agents in combination with other chemotherapeutic or biological agents.
- New data on the mechanisms of resistance and strategies to enhance delivery, permeability and stability *in* vivo of platinum agents have *ca*used a **research resurgence**.
- The ability to monitor their pharmacokinetics using their Pt radioisotopes, *in vitro* and *in vivo* would be an invaluable tool for theranostic imaging. Platinum radioisotopes can be produced by neutron, proton and deuteron bombardment of Pt, Ir and Au.
- Proton bombardment of Pt metal produces large number of Pt, Au, Ir, Re &Os radionuclides - Proton cross section on platinum metal are only reported to 70 MeV.
- Using high energy protons at BLIP provides an opportunity to study new paths for radioisotope production and the validation of EMPIRE modelling methods.
- Optimizing energy for production of desired Platinum Isotopes requires:
    - *Good chemical separation methods.*
    - *Superior gamma spectrometry – compton suppressed and*
    - *EMPIRE calculations*

Platinum foils irradiated at 193.4 and 107.4 MeV at BLIP

^{Nat}Pt
Irradiate with 193.4 and 107.4 MeV Protons for 1.7 hrs

Aqua regia (HCl/HNO_3)

$H_2{}^{195m}PtCl_6$ — ***Pt(IV)***

NaCl

$Na_2{}^{195m}PtCl_6$

Hydrazine

Pt(II)

$^{195m}PtCl_4$

KI

$^{195m}PtI_4$

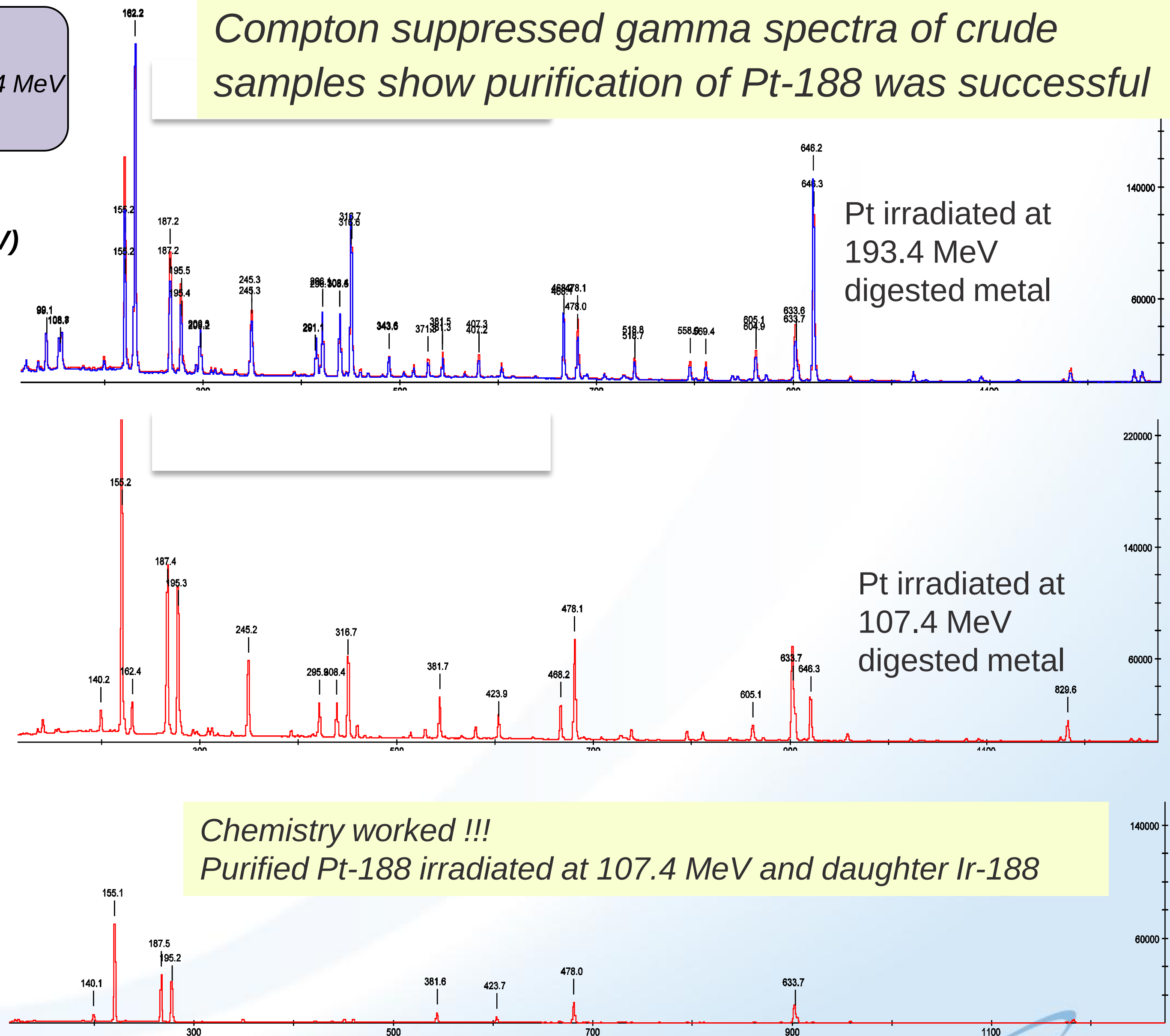
NH_4OH

$^{195m}Pt(NH_3)_2I_2$

$AgNO_3$

$^{195m}Pt(NH_3)_2(H_2O)_2$

Compton suppressed gamma spectra of crude samples show purification of Pt-188 was successful



Chemistry worked !!!
Purified Pt-188 irradiated at 107.4 MeV and daughter Ir-188

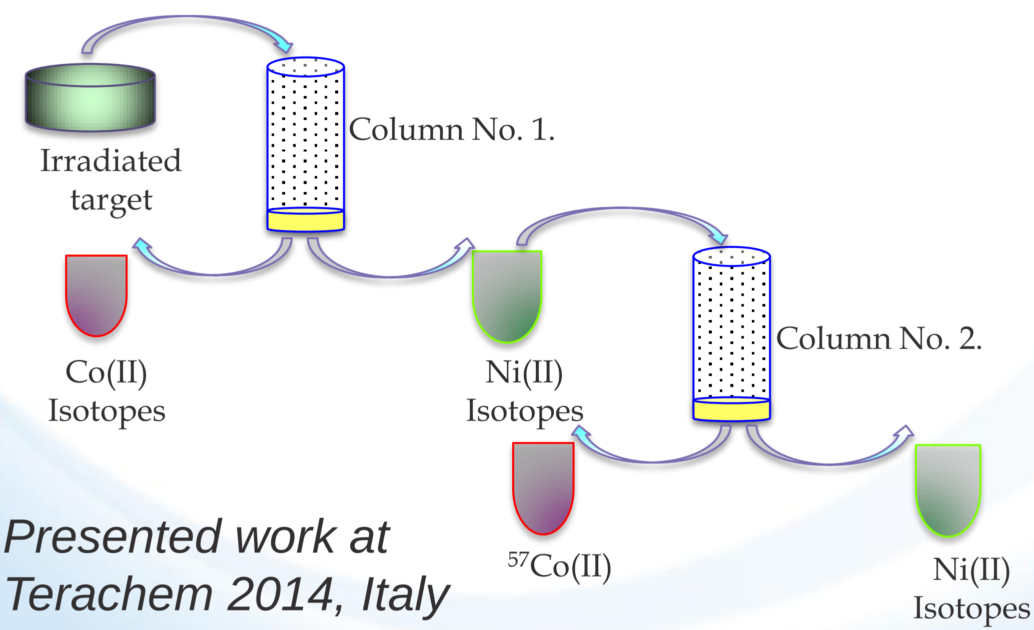
Co-57 – New separation method

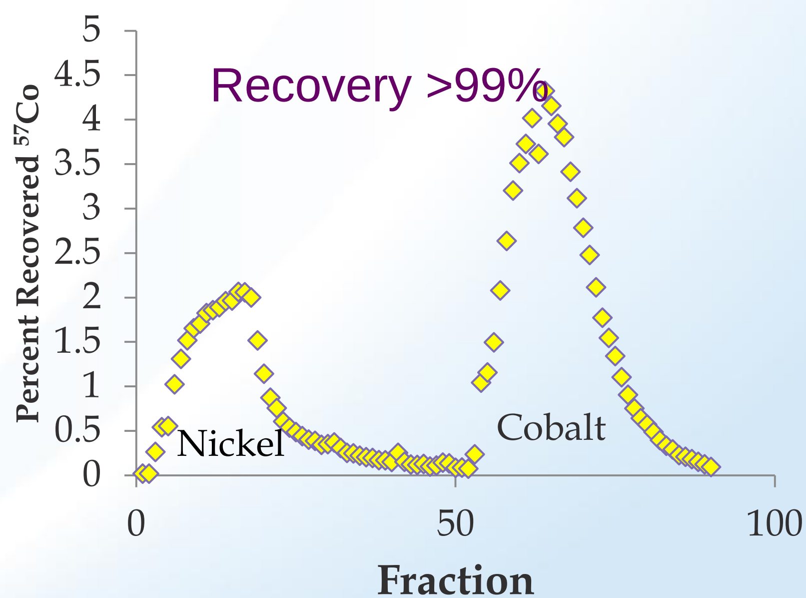
Suzanne V Smith and DOE summer intern Zac Gotlib

Cobalt-57 is used to calibrate nuclear instrumentation ($t_{1/2}$ = 271.74 days; ideal gammas 122 keV (85.6 %) and 136 keV (10.7 %)

Produced via $^{nat}Ni(p,x)^{57}Co$ or ^{57}Ni

New separation method that uses organic acid mixtures.



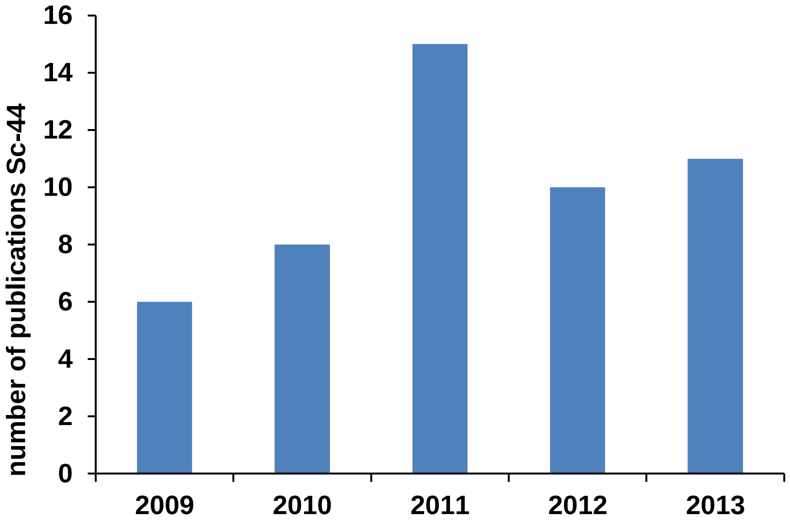


Presented work at Terachem 2014, Italy

Planned R&D FY15-19

- Develop As-72 & Cu-67 FOA funded 7/13 – S. Smith PI
- Basic radiochemistry development FOA funded 11/14 – J. Fitzsimmons PI
- Ti-44/Sc-44 – D. Medvedev PI
- Pt-188, 191,193m – S.Smith PI
- Re-186 ($t_{1/2}$=3.7d) for radioimmunotherapy –S. Smith PI
  - Develop W and Os based targets in collaboration with Missouri U. for low energy irradiation at BLIP
- Ag-111, Rh-105, and other isotopes of potential interest coproduced by fission of Th

Scandium-44 – sustained interest



Institutions to name a few:

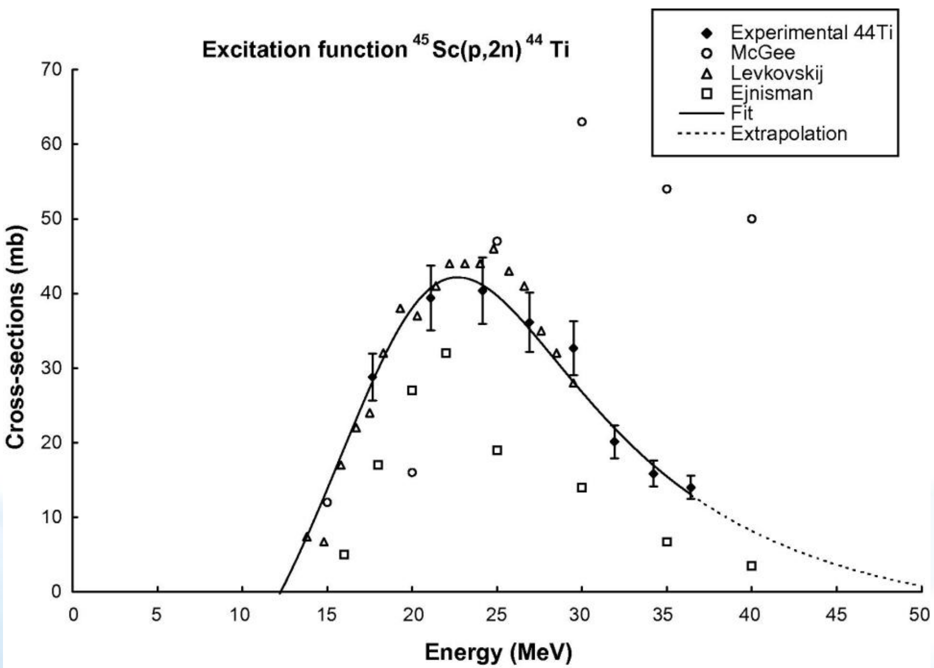
- Institute of Nuclear Chemistry, University of Mainz, Mainz, Germany - ***generator approach and labeling***
- University of Wisconsin, Department of Medical Physics, Madison, WI, USA – ***direct production***
- Hungarian Academy of Sciences, Institute of Nuclear Research, Debrecen, Hungary - ***cross section measurements***
- ***and others***

- Sc-44 is a PET emitter
  - Decays by electron capture to Ca-44 (stable), mean $E_{\beta+}$=632 keV, Eγ=1157.02 keV (99.9%)
  - Metallic isotope that offers intermediate half-life of 3.97 h (Ga-68 – 67.7 min, Zr-89 – 78.41 h)
  - Theranostics*
    - Pre-therapeutic dosimetry evaluation for M^{3+} -radiopharmaceuticals
    - Possibility to use as a diagnostic pair for therapeutic Sc-47

* From F. Roesch, *Current Radiopharmaceuticals*, 2012, 5, 187-201

Low energy $^{45}Sc(p,2n)^{44}Ti$ nuclear reaction*

- Direct production with $^{44}Ca(p,n)^{44}Sc$ reaction
  - Short half-life limits distribution, expensive enriched target and needed proton energy <13 MeV not suitable for BLIP due to energy straggle



- Reaction on natural Sc preferred
- Low energy reaction challenges:
  - Heat load and dissipation over long term irradiation
    - 0.125 inch of Sc metal is required to degrade energy from 28 to 14 MeV
    - Sc melting point 1541^{0}C
    - Sc thermal conductivity 15.8 W/(m*K) (~200 for Al)
  - Sc metal cost: ~$1600 for $2 .75 \times$ $\times 0.1$ inch target
  - Accuracy of the predicted energy on the low energy target remains uncertain but high purity of Ti-44 easy to attain due to 59.9 yr half life.

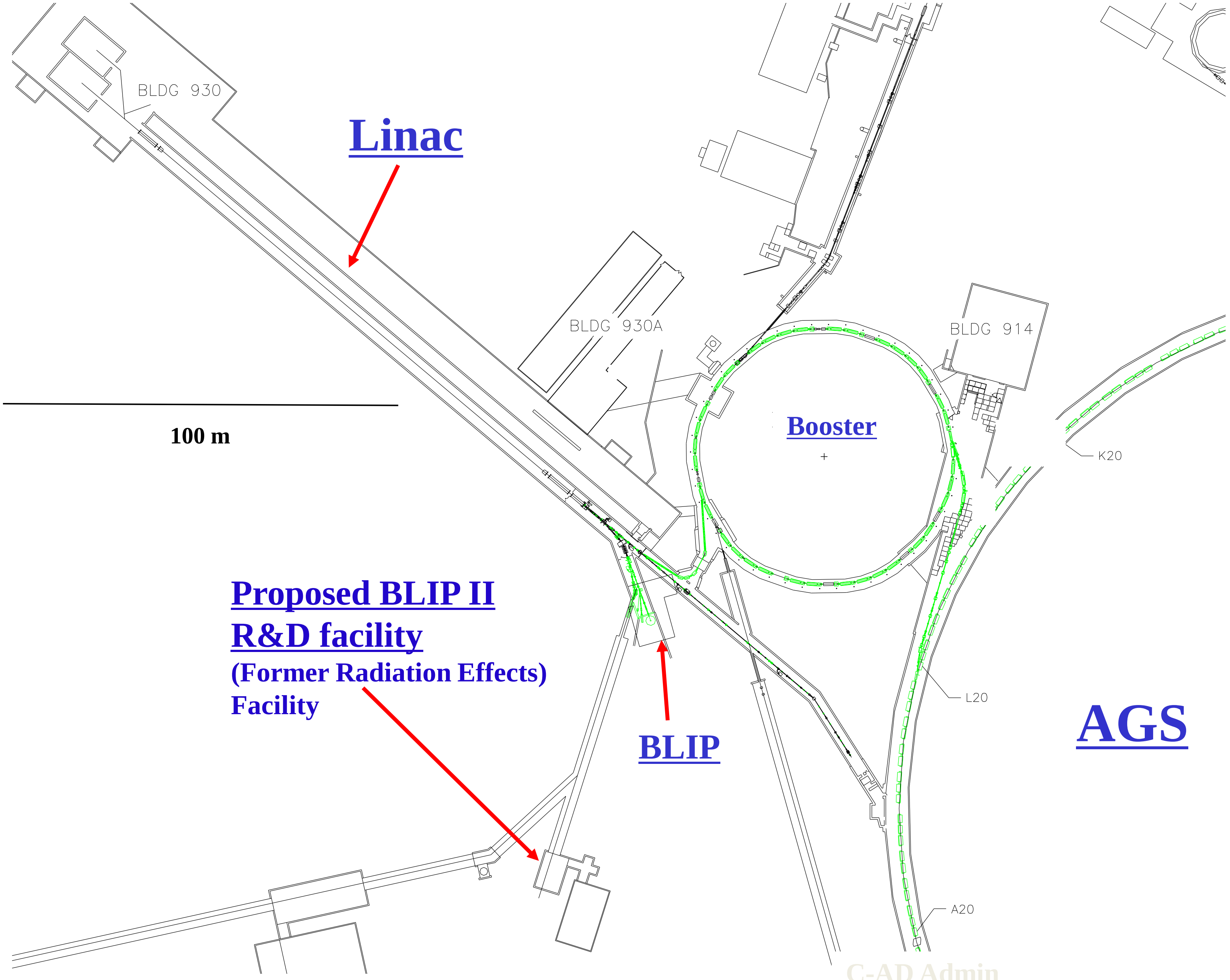
* Excitation functions from Daraban et al., ***Nucl. Inst. Meth. Phys. Res*. *B***, 2009, 267 (5), 755

Technical approach

- Long duration Irradiation in the low energy slot – could be used as a beam stop
- Yield ~0.1 µCi/µA-h
  - 8.2 mCi generator in 1 month of beam time, 65 mCi generator in one season at BLIP
- Indefinite lifetime of the generator
  - Pre-loaded generator distribution
  - Potential for business in generator development for larger quantities of Ti-44
  - Ti-44 recovery and reloading activities can be done at DOE sites: LANL and BNL
- Collaborative effort with LANL
  - FY 2015 Joint development of Ti-44/Sc separations– share target solutions
  - FY2015-FY2016 generator development and testing
- BNL effort for FY2015
  - A small aliquot from the dissolution of the first LANL target will be shipped to BNL in November for chemistry development
  - Three research irradiations will be carried out at BLIP
    - two short irradiations to test chemical processing and validate energy degradation
    - Third irradiation to produce 8 mCi of Ti-44 for generator development and testing

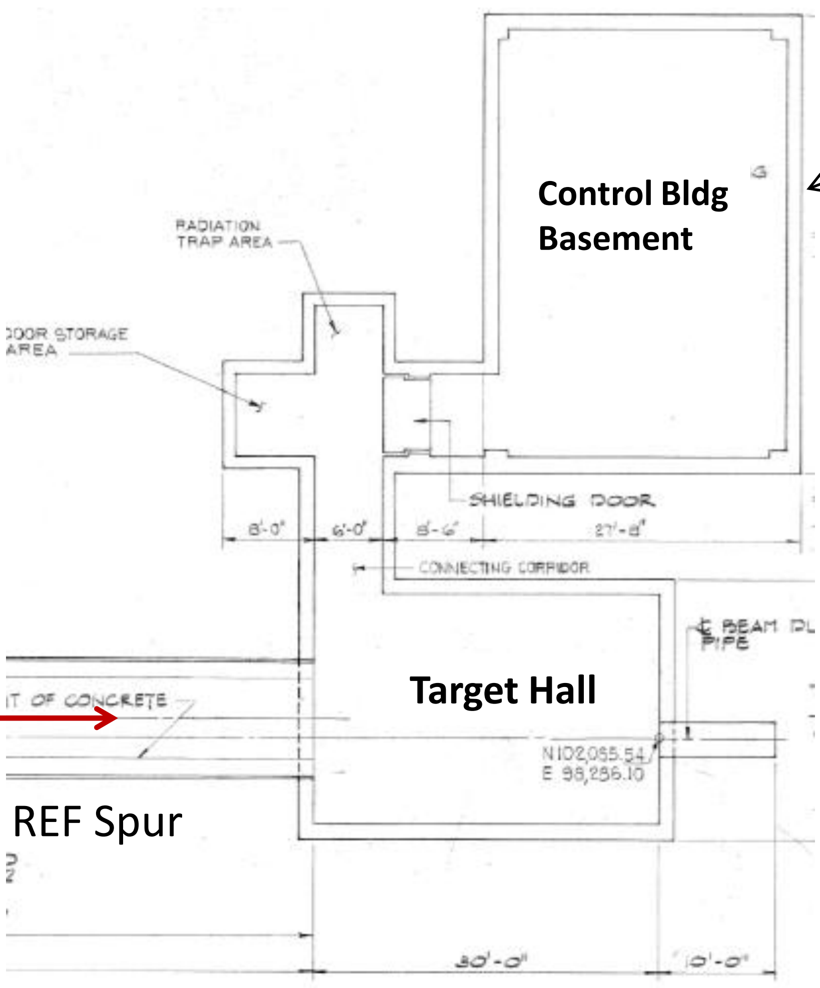
Long term initiative – second beam line and target station

- There is a defunct beamline and target station, previously called the Radiation Effects Facility (REF), that is a spur off the BLIP beam line.
- As a follow on to the Raster and Linac I&II upgrades, we are considering installation of a second BLIP beam line and target station in this existing infrastructure.
    - The REF area is larger than BLIP and can easily accommodate a hot cell for target insertion/removal, as well as power supply racks, control system electronics, target cooling system, storage space and an office.
- This target station could operate simultaneously with BLIP but at a different and lower proton energy, spanning 37-200 MeV.
    - This eliminates the competition for beam time that currently exists between R&D irradiations that are incompatible with on going routine production.
    - Pulse by pulse energy switching capability in the Linac already exists and is routinely used to accommodate both BLIP and RHIC needs.
- If all projects are funded and completed BLIP would have the unmatched capability to simultaneously irradiate 8-16 targets at energies from 37-200MeV at intensities up to 240μA. The rough order of magnitude cost is $22M (FY14 $).


BLDG 930
Linac
BLDG 930A
BLDG 914
100 m
Booster
K20
Proposed BLIP II
R&D facility
(Former Radiation Effects)
Facility
BLIP
L20
AGS
A20

Radiations Effect Facility Target Hall and Control Building

27' X 40' building



Beam from Linac REF Spur

Supplemental slides

Ac-225 separation development

(General List of completed Experiments and general findings)

1. Which pH of the load solution results in the best lanthanum recovery?

   pH 1.5-2.5 - optimal pH chosen pH=2.0 for both citric and tartaric acid

2. Which of the evaporation steps are necessary?

   >65% of La found in Load solutions -evaporation of dissolved thorium target necessary if dissolved in a concentrated acid

3. Which acid is best for the selective elution of La and optimization of rinse steps?

   Rinses with Nitric, Sulfuric and Hydrochloric acid were tested

   A combination of rinses with Hydrochloric acid followed by Nitric acid are optimal to remove impurities

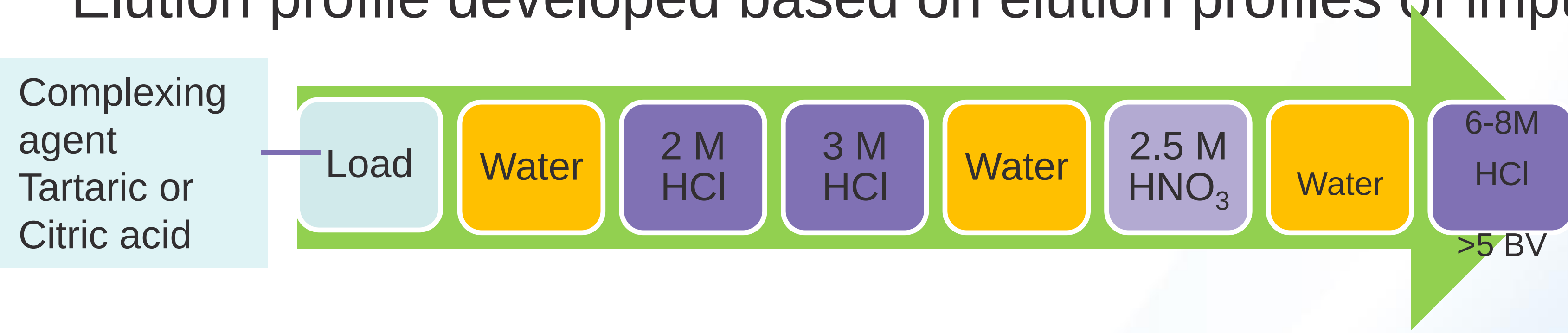
4. Is retention/elution of La the same on AG-50 resins and the MP-50?

   Elution profiles of AG-50 and MP-50 were not the same

Ac-225 separation development

Task: Examine Cation exchange resin ability to capture Ac-225/La from bulk Th and other impurities.

Elution profile developed based on elution profiles of impurities



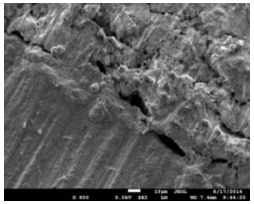
- >13,000 data points collected on behavior of La and other metals with cation resin, two complexing agents and load/rinse/elution steps

BLIP Irradiation Studies

(a) 200 MeV Proton Irradiation
(b) Spallation Neutron Irradiation

Objective:

Study Radiation Damage in materials considered in next generation reactors and particle accelerators

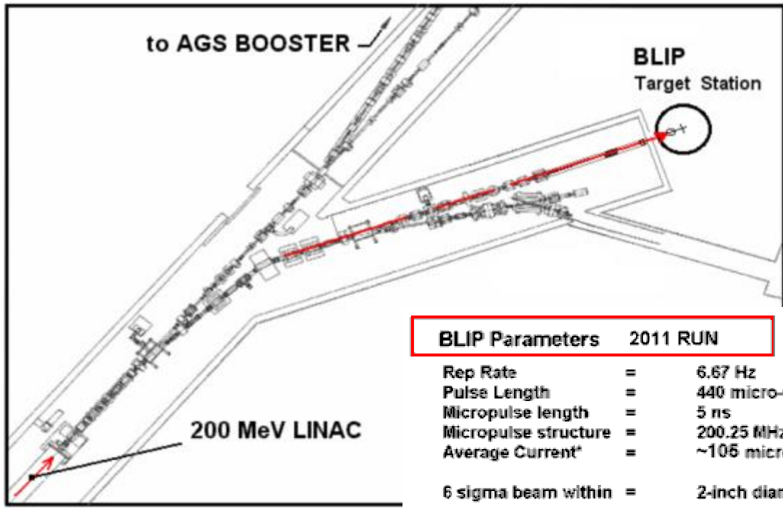


Next Generation Fusion and Fission Reactors: Exploration of radiation tolerance of super-alloys, graphite, silicon fiber composites, copper alloys and tungsten based on spallation-generated fast and thermal neutrons

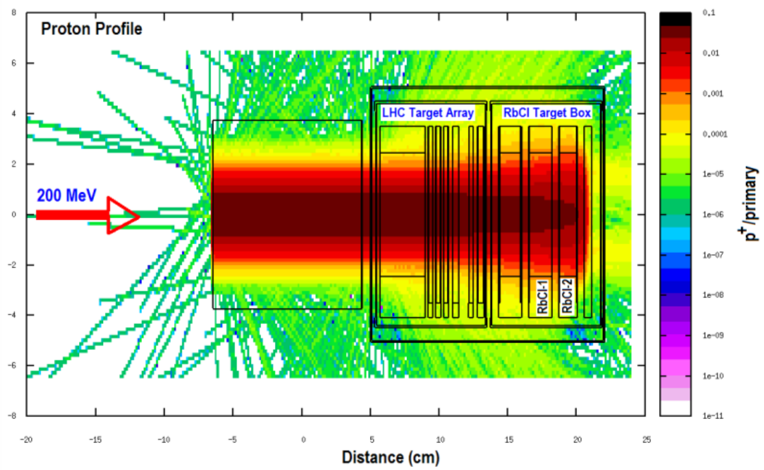
Particle Accelerators (Large Hadron Collider and Long Baseline Neutrino)
Study of the radiation-induced changes in high power target and collimation materials using energetic protons (180-200 MeV) from Linac

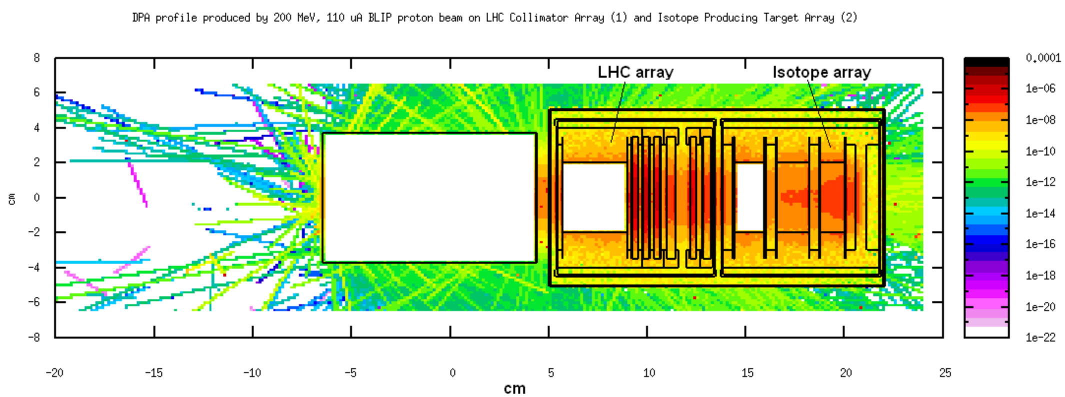
Post-Irradiation Evaluation (PIE): Utilizing experimental capabilities and expertise at the Isotope Extraction Facility and the BNL Synchrotron Light Source

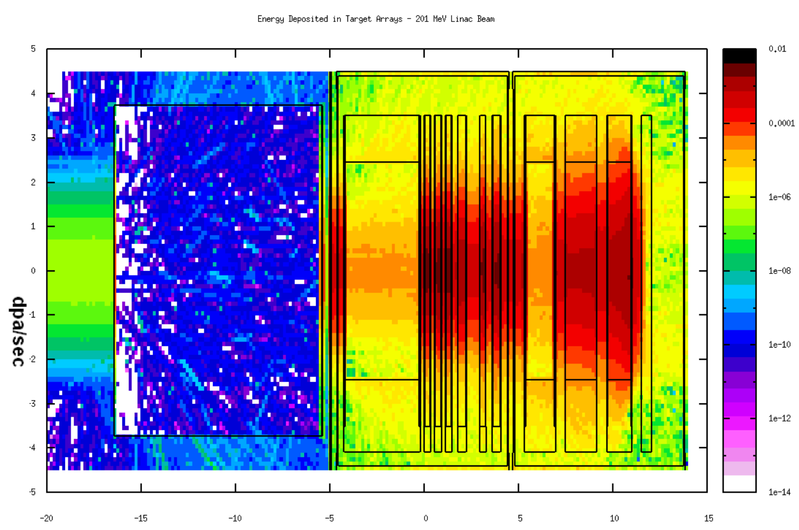
BLIP Irradiation Studies – 180-200 MeV Proton Irradiation



BLIP Parameters		2011 RUN
Rep Rate	=	6.67 Hz
Pulse Length	=	440 micro-secs
Micropulse length	=	5 ns
Micropulse structure	=	200.25 MHz
Average Current*	=	~105 micro-A
6 sigma beam within	=	2-inch diameter
Beam Gaussian	==>	1 sigma = 4.233 mm







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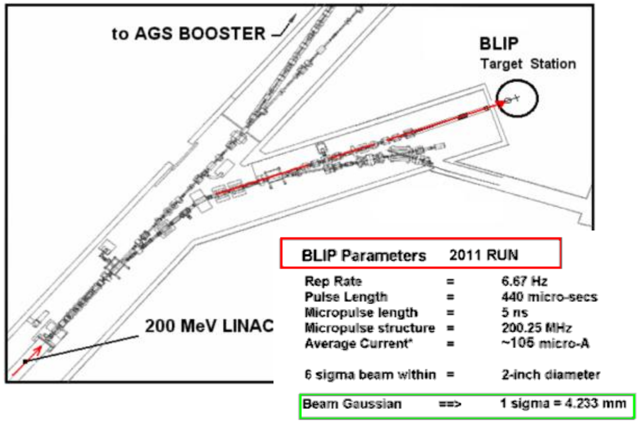
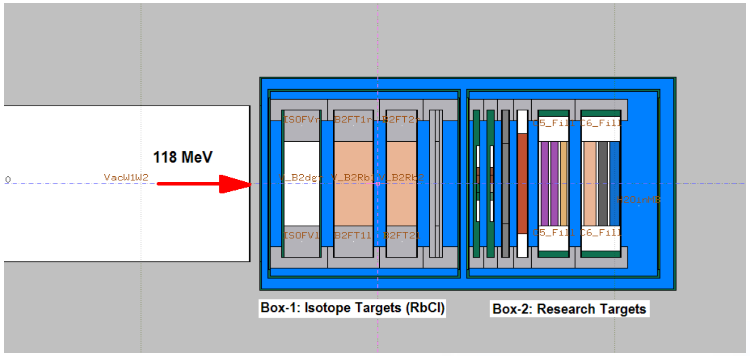
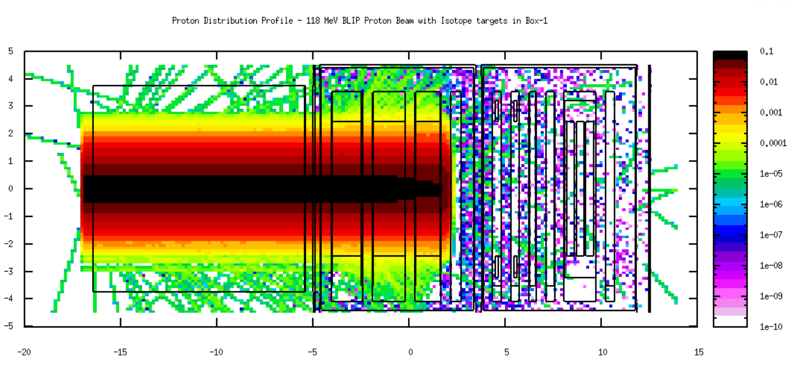
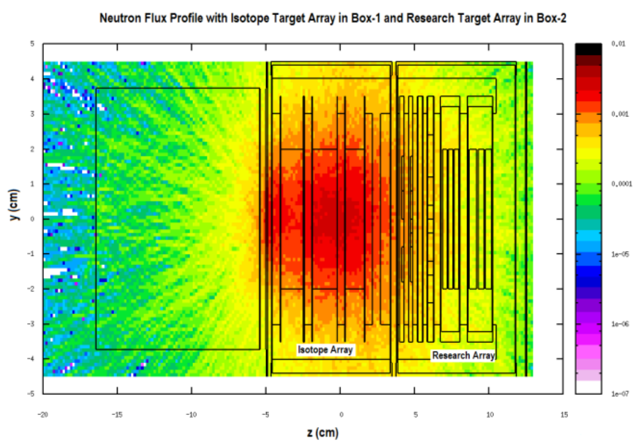
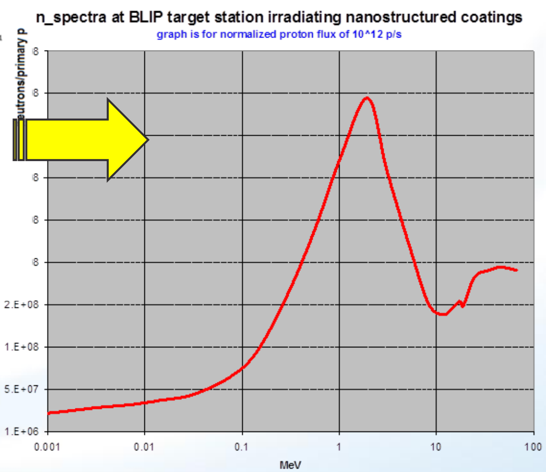


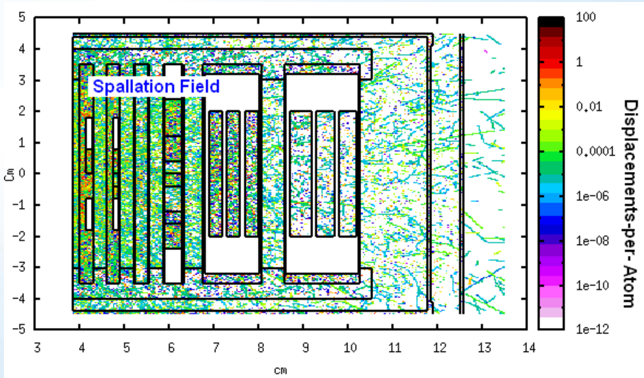






Neutron spectrum downstream of isotope target array





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